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(54) COMPOSITION PHARMACEUTIQUE POUR APPLICATION INTRANASALE COMPRENANT DES ANTAGONISTES CGRP SELECTIONNES DERIVES D'ACIDES AMINES ET PROCEDE POUR LES PREPARER

(54) PHARMACEUTICAL COMPOSITION FOR THE INTRANASAL APPLICATION CONTAINING SELECTED CGRP ANTAGONISTS DERIVED FROM AMINO ACIDS AND PROCESS FOR PREPARING THEM

(57)

The invention relates to pharmaceutical compositions for nasal application, comprising selected CGRP antagonists, which are described in WO 98/11128, in addition to a method for their production.

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(54) Titre : PREPARATIONS POUR APPLICATION INTRANASALE D'ANTAGONISTES DE CGRP SELECTIONNES, DERIVES D'ACIDES AMINES, ET PROCEDE POUR LES PREPARER

(54) Title: PREPARATIONS FOR THE INTRANASAL APPLICATION OF SELECTED CGRP ANTAGONISTS DERIVED FROM AMINO ACIDS AND A METHOD FOR THEIR PRODUCTION

(57) Abrégé/Abstract:
The invention relates to pharmaceutical compositions for nasal application, comprising selected CGRP antagonists, which are described in WO 98/11128, in addition to a method for their production.

Abstract

The invention relates to pharmaceutical compositions for nasal application, comprising selected CGRP antagonists which are described in WO 98/11128, as well as a process for the preparation thereof.

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Pharmaceutical composition for the intranasal application containing selected CGRP antagonists derived from amino acids and process for preparing them

The invention relates to pharmaceutical compositions for nasal administration containing selected CGRP-antagonists which are described in WO 98/11128, as well as a process for preparing them.

The compounds designated (A) to (CJ) hereinafter have CGRP-antagonistic properties and exhibit very good affinities in CGRP-receptor binding studies.

The following compounds, in the form of their salts with physiologically acceptable acids dissolved in water, may be used as constituents of the nasal preparations according to the invention:

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazoline-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine,

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine,

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine,

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine,

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine,

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine,

(V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine,

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine,

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine,

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine,

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AD) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N^2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine,

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)carbonyl]-piperidine,

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepines-1-yl)piperidine,

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine,

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BC) 1-[N^6-acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine,

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine,

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine,

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropylmethyl)-4-piperidinyl]-piperidine,

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine,

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine,

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BW) 1-[N2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BY) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CB) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine,

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine,

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine,

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

the tautomers, diastereomers, enantiomers and mixtures thereof.

Prior art

The compounds of the abovementioned group (A) to (CJ) are highly effective CGRP antagonists for treating migraine which cannot be administered orally in conventional formulations as the substance has very limited bioavailability by the oral route both as an active substance base and in the form of its salts.

Oral administration of an active substance is generally the most practical form for the patient. As acute migraine attacks are often accompanied by nausea and vomiting, however, oral administration of an anti-migraine drug may be difficult or even impossible.

In an acute migraine attack it is essential that the effect of the drug taken should set in immediately or at least soon after it is taken, which means that

effective plasma levels should advantageously be achieved shortly after administration. The possibilities in connection with this would be intravenous, intramuscular or subcutaneous administration by injection. This complex procedure, particularly as it involves an increased risk of infection, is not suitable for general use, however.

As an alternative to absorption through the gastrointestinal tract the nasal mucosa constitute a surface which is theoretically equally suitable for the absorption of medicaments. In the nasal epithelium the biotransformation of drugs is substantially less marked than in the gastrointestinal tract or in the liver, so that rapid absorption of suitable active substances into the bloodstream and the absence of a first-pass metabolism can be expected. Under these conditions it ought to be possible rapidly to obtain high plasma levels similar to those obtained by injection.

Conventional nasal applications use propellants to ensure satisfactory administration. As a rule, standard commercial propellants are chlorofluorohydrocarbons as well as fluorohydrocarbons, which makes formulations of this kind problematic in terms of environmental protection.

Aqueous formulations in pump or valve sprays which can be used without propellants have to be made durable by the addition of preservatives. However, preservatives are linked with a high allergy potential, which is why allergy sufferers cannot use these pharmaceutical compositions. In addition all the permitted preservatives are cytotoxic and affect ciliary function and hence also clearance.

Another disadvantage of the nasal absorption of active substances from aqueous solutions is their pH dependency. The optimum medium for the cilia of the nasal mucosa is a pH of 7 to 9. However, maximum absorption is achieved at a pH below 6.

Statement of the Problem

The objective of the present invention was to provide a rapidly bioavailable formulation for the abovementioned highly active CGRP antagonists (A) to (CJ), by means of which the problem of low oral availability is circumvented. The formulation according to the invention should have a rapid onset of activity for treating acute pain which sets in very suddenly in migraine. This means that a rapid uptake of the active substance and a fast rise in the plasma level have to be guaranteed. The formulation according to the invention should be available in a form which also allows it to be used to treat migraine attacks that happen only sporadically. In addition, the susceptibility of the active agent to oxidative decomposition throughout the storage time of the product should be borne in mind when designing effective protection against oxygen.

Description of the invention

A high plasma level of active substances (A) to (CJ) and hence a rapid onset of activity for the treatment of acute pain in the shortest time possible can be achieved not only by intravenous administration but also via the nose as the organ of administration according to the invention.

Within the scope of the present invention it has now surprisingly been found that the CGRP antagonists (A) to (CJ) according to the invention may be made sufficiently bioavailable by administration via the nose in the form of their salts with physiologically acceptable solubilising acids, preferably their salts with hydrochloric acid in the form of the hydrochlorides.

A first object of the invention is therefore a pharmaceutical composition for nasal application in the form of an aqueous solution, comprising

(a) 2% to 25 % w/v, preferably 10% to 20% w/v of an active substance, selected from the group (A) to (CJ) consisting of

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine,

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine,

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine,

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine,

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine,

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine,

(V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine,

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine,

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine,

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine,

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxo-butyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AD) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-di-oxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N^2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxo-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine,

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)carbonyl]-piperidine,

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl)-piperazine,

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepines-1-yl)piperidine,

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine,

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BC) 1-[N^6-acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine,

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine,

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine,

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropylmethyl)-4-piperidinyl]-piperidine,

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine,

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine,

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BW) 1-[N2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BY) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CB) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine,

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine,

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine,

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine, and

(b) at least one equivalent of a physiologically acceptable solubilising acid, the active substance being converted by means of the acid into the corresponding salt and being dissolved in anionic form.

A preferred embodiment according to the invention contains the compounds

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine or

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine.

To solubilise the active substance bases, which have only limited solubility, they are reacted with an at least equimolar amount, preferably with 1.2 to 2 equivalents, more preferably with 1.6 to 1.9 equivalents, of an acid *in situ* to obtain the corresponding acid addition salt. In one particularly preferred embodiment of the invention the active substance is reacted with 1.75 equivalents of acid.

In this way, even highly concentrated solutions can be produced, but their use by the nasal route is restricted by the fact that their viscosity which increases with the concentration makes it difficult if not impossible to produce a fine spray mist with a suitable spray geometry ("plume") or with a suitable particle size. Suitable inorganic and organic physiologically acceptable acids are for example hydrochloric acid, phosphoric acid, methanesulphonic acid, acetic acid, formic acid or succinic acid.

Surprisingly it has been found that the molar ratio of active substance base to solubilising acid affects the miscibility of the weakly acidic active substance solution with physiological body fluids such as plasma or nasal mucus, so that the active substance remains in solution in the physiological, neutral pH range longer or in a higher concentration the higher the molar excess of solubilising acid. A longer delay time of the active substance in dissolved form on the nasal mucosa should therefore lead to a higher absorption rate and higher systemic availability.

Another pharmaceutical composition according to the invention may therefore also contain a physiologically acceptable salt of the abovementioned active substances of group (A) to (CJ) in an aqueous solution of the concentrations specified above, to which 0.2 to 1 equivalents, preferably 0.6 to 0.9 equivalents, of the corresponding acid are added.

A particularly preferred embodiment contains hydrochloric acid as the solubilising acid in an excess of 0.75 molar equivalents based on the active substance base used.

Another embodiment according to the invention of a pharmaceutical composition for nasal administration additionally contains one or more "absorption enhancers" such as e.g. caprylocaproyl-macrogolglyceride (Labrasol ™) or lysolecithin in a concentration of 0.1% to 5% w/v, preferably in the range from 0.5% to 3% w/v. This absorption enhancer increases the permeability of the mucosa, eventually resulting in a higher systemic availability of the active substance.

Another embodiment according to the invention of a pharmaceutical composition for nasal administration additionally contains a gel-forming agent such as e.g. hydroxypropylmethyl-cellulose, polymers of acrylic acid (e.g. Carbopol 934) or xanthan in a concentration of 0.05% to 1% w/v, preferably in the range from 0.1% to 0.5% w/v. This increases the viscosity and hence the retention time of the nasally administered preparation by modifying the "clearing mechanism" of the nasal mucosa.

Another embodiment of the nasal preparation additionally contains a liposome-forming phospholipid, e.g. soya lecithin S 100, in a concentration of 2% to 10% w/v, preferably in the range from 3% to 8% w/v, optionally additionally containing a small amount of a phospholipid-hydrolysis product, e.g. lysolecithin, in a concentration of 0.5% to 1% w/v. The liposome-based formulation has a higher permeation rate through the mucosa and therefore the active substance has a high systemic availability.

Moreover, one or more isotonic agents may optionally be added to the abovementioned embodiments according to the invention, for example sodium chloride in concentrations of 0.3% to 3% w/v, mannitol in concentrations of 1.5% to 15% w/v, lactose in concentrations of 3% to 20% w/v or xylitol in concentrations of 1.5% to 15% w/v.

The preparations according to the invention are preferably packaged and administered as single doses which means that preservation, recognised as disadvantageous, can be dispensed with. Moreover, this does not provoke any decomposition of the oxygen-sensitive preparation and avoids the need to specify a relatively short shelf life. In addition, the condition of migraine does not require regular or long-term use which would justify packaging the substance in a multi-dose container; rather, the pharmaceutical composition is used only in (acute) cases of need. The patient can take the drug at any time, depending on the individual nature of the migraine, e.g. the frequency, trigger factors, etc, and his/her individual custom, using a single dose preparation a number of which may be kept handy "for emergencies" in pockets, handbags, in the car, etc. Suitable primary packaging agents include, for example, a commercially available, tried and tested single dose system produced by Messrs Pfeiffer, Radolfzell (UDS = unit dose system).

The marked susceptibility of the active substance solution to oxygen imposes special requirements on the manufacture and packaging. The addition of antioxidants such as sodium metabisulphite or propyl gallate etc. should be avoided for reasons of tolerance, e.g. to avoid allergic reactions. Instead, during manufacture, the solution may be subjected to submersion or surface-gassing with a protective gas, e.g. nitrogen or argon or a combination thereof. Similarly, during packaging, the primary container may subjected to pre- and post- gassing. With regard to the possibility of producing large numbers of items, it is possible to use equipment similar to that used for conventional ampoule filling, while particular importance is attached to efficient protective gassing with one of the abovementioned inert gases and to the quality and positioning of the closure of the primary container, e.g. a rubber stopper, to bring the residual oxygen content in the primary container down to levels below 1%, preferably below 0.5%.

As has been shown in real-time storage experiments, even the measures described above are still not sufficient to protect the product long-term against oxidation over its entire shelf-life.

Thus, in another aspect, the present invention relates to the identification of a secondary packaging which provides this long-term protection. Suitable packages are bag or tubular bag packages made of aluminium or metallised films, if filled with the primary packaging means (e.g. UDS) under a protective gas atmosphere and heat-sealed. Another alternative is packaging in transparent films provided that sufficient long-term protection can be achieved with transparent films by the inclusion of oxygen absorbers (e.g. those which contain powdered elementary iron or iron oxide which absorbs oxygen, forming iron oxide at various stages of oxidation of the iron).

A second object of the invention is a process for preparing one of the pharmaceutical compositions mentioned above, comprising the steps of

(a) dissolving 2 to 25% w/v, based on the pharmaceutical composition, of an active substance selected from the group (A) to (CJ) according to claim 1 in an aqueous solution, comprising at least one equivalent of a physiologically acceptable solubilising acid or

(b) dissolving a salt of an active substance selected from the group (A) to (CJ) according to claim 1, formed with a physiologically acceptable solubilising acid, in water in an amount such that the active substance content of the composition based on the active substance is 2% to 25% w/v, and optionally

(c) adding excess physiologically acceptable solubilising acid and

(d) optionally adding one or more excipients, selected from absorption enhancers, gel-forming agents and liposome-forming phospholipids as well as

(e) optionally packaging the resulting solution under protective gas as single doses in primary packaging means, the primary packaging means being placed in a secondary package in the

form of a bag or tubular bag packaging made of aluminium, metallised film or transparent film, under a protective gas atmosphere, optionally together with an oxygen absorber.

Experimental Data

(1) Stability

Stability testing of more highly concentrated nasal spray solutions according to the invention:

The following Table shows that the oxidative decomposition of the active substance listed below

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

in the form of the hydrochloride in aqueous solution is virtually unchanged or increases only slightly over a long period. The total decomposition which is high in some circumstances (particularly at 40°C) is based on hydrolysis.

The content of active substance (A) given in Table 1 refers in each case to the free base originally weighed out.

Table 1:

Active substance concentration			15 %	20 %	30 %
Storage time	**Storage temp:**	**Test points**			
Initial value		content of active substance (A)	148.6mg/ml	197.9mg/ml	269mg/ml
		decomposition by oxidation	0.59%	0.56%	0.56%
		overall decomposition	1.23%	1.27%	1.20%
		oxygen content in aluminium bag	0.3%	0.3%	0.9%
6-week value	**25°C**	content of active substance (A)	148.1mg/ml	198.7mg/ml	264mg/ml
		decomposition by oxidation	0.72%	0.54%	0.62%
		overall decomposition	1.60%	1.09%	1.19%
		oxygen content in aluminium bag	0.3%	0.2%	0.4%
	40°C	content of active substance (A)	142.3mg/ml	192.1mg/ml	260mg/ml
		decomposition by oxidation	0.52%	0.55%	0.58%
		overall decomposition	4.46%	3.97%	3.95%
		oxygen content in aluminium bag	0.3%	0.6%	0.4%
3-month value	**25°C**	content of active substance (A)	147.7mg/ml	202.8mg/ml	270mg/ml
		decomposition by oxidation	0.64%	0.53%	0.60%
		overall decomposition	1.69%	1.50%	1.48%
		oxygen content in aluminium bag	0.4%	0.3%	0.3%
	40°C	content of active substance (A)	139.4mg/ml	191.4mg/ml	260mg/ml
		decomposition by oxidation	0.55%	0.47%	0.59%
		overall decomposition	8.22%	8.23%	7.81%
		oxygen content in aluminium bag	0.4%	0.6%	0.3%
6-month value	**25°C**	content of active substance (A)	147.7mg/ml	201.8m/ml	273mg/ml
		decomposition by oxidation	0.82%	0.77%	0.91%
		overall decomposition	2.07%	1.99%	2.04%
		oxygen content in aluminium bag	0.7%	0.4%	0.4%
	40°C	content of active substance (A)	131.7mg/ml	182.8mg/ml	246mg/ml
		decomposition by oxidation	0.78%	0.74%	0.84%
		overall decomposition	15.33%	14.61%	13.36%
		oxygen content in aluminium bag	0.4%	0.5%	0.4%

(2) Pharmacokinetics

The following Table 2 shows the absolute bioavailability of various formulations according to the invention of 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine after intranasal administration to Cynomolgus monkeys from AUC data, standardised to 1.0 mg/kg of body weight.

Table 2:

Formulation	**Abs. Bioavailability [%]**
aqueous solution, 1 molar equivalent HCl	4.8%
aqueous solution, 1.75 molar equivalents HCl, with Labrasol (1.5%)	7.2%
aqueous solution, 1.75 molar equivalent HCl, with Labrasol (3%)	8.2%
aqueous solution, 1.75 molar equivalents HCl	7.8%
liposome formulation (5% Lipoid S100, 1% lysolecithin, 1.75 molar equivalents HCl)	13.2%

(3) Examples

Example 1: Aqueous solution; 10% active substance; 1.75 molar equivalents HCl

BIBN 4096		10	mg
1N HCl		20.45	mg
Mannitol		5	mg
water	ad	0.1	ml

Method:
The calculated amount of hydrochloric acid is added to water, the active substance is dissolved with stirring and optionally heating. The isotonic agent mannitol is added and the solution is topped up to the final volume with water.

Example 2: Aqueous solution; 25% active substance; 1.75 molar equivalents HCl

BIBN 4096		25	mg
1N HCl		51.12	mg
Mannitol		5	mg
water	ad	0.1	ml

Method:
The calculated amount of hydrochloric acid is added to water, the active substance is dissolved with stirring and optionally heating. The isotonic agent mannitol is added and the solution is topped up to the final volume with water.

Example 3: Aqueous solution; 20 % active substance, 1.5 % Labrasol; 1.75 molar equivalents HCl

BIBN 4096		20 mg
1N HCl		40.9 mg
Labrasol		1.5 mg
Mannitol		5 mg
water	ad	0.1 ml

Method:

The calculated amount of hydrochloric acid is added to water, the active substance is dissolved with stirring and optionally heating. The isotonic agent mannitol and the Labrasol are added and the solution is topped up to the final volume with water.

Example 4: Aqueous solution; 10% active substance, 3 % Labrasol; 1.75 molar equivalents HCl

BIBN 4096 BS		10 mg
1N HCl		20.45 mg
Labrasol		3 mg
Mannitol		5 mg
water	ad	0.1 ml

Method:

The calculated amount of hydrochloric acid is added to water, the active substance is dissolved with stirring and optionally heating. The isotonic agent mannitol and the Labrasol are added and the solution is topped up to the final volume with water.

Example 5: Liposomes; 5% active substance; 1.75 molar equivalents HCl

BIBN 4096	5	mg
1N HCl	10.2	mg
Soyalecithin (Lipoid S 100)	5	mg
Mannitol	4.5	mg
water ad	0.1	ml

Method:

The calculated amount of hydrochloric acid is added to water, the active substance is dissolved with stirring and optionally heating. The isotonic agent mannitol is added, the soyalecithin is added. After predispersion, e.g. with an Ultra-Turrax, liposomes are produced using a high pressure homogeniser with a specific number of cycles and a specific pressure.

Patent Claims

1. Pharmaceutical composition for nasal application in the form of an aqueous solution, comprising

(a) 2% to 25 % w/v, preferably 10% to 20% w/v of an active substance, selected from the group (A) to (CJ) consisting of

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine,

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine,

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine,

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine,

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine,

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine,

(V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine,

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine,

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine,

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine,

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AD) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N^2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine,

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)carbonyl]-piperidine,

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl)-piperazine,

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepines-1-yl)piperidine,

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine,

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BC) 1-[N^6-acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine,

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine,

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine,

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropylmethyl)-4-piperidinyl]-piperidine,

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine,

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine,

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BW) 1-[N2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BY) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CB) 1-[4-amino-N-[[4-[4-(3-chlorphenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine,

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine,

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine,

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine, and

(b) at least one equivalent of a physiologically acceptable solubilising acid, the active substance being converted by means of the acid into the corresponding salt and being dissolved in anionic form.

2. Pharmaceutical composition according to claim 1, comprising in aqueous solution 10 to 20 wt.% of an active substance from group (A) to (CJ).

3. Pharmaceutical composition according to claim 1 or 2, comprising in aqueous solution 1.2 to 2 equivalents of a physiologically acceptable, solubilising acid.

4. Pharmaceutical composition according to claim 1 or 2, comprising in aqueous solution 1.6 to 1.9 equivalents of a physiologically acceptable, solubilising acid.

5. Pharmaceutical composition according to one of claims 1 to 4, characterised in that the physiologically acceptable, solubilising acid used is selected from the group consisting of hydrochloric acid, phosphoric acid, methanesulphonic acid, acetic acid, formic acid and succinic acid.

6. Pharmaceutical composition according to one of claims 1 to 4, characterised in that the physiologically acceptable, solubilising acid used is hydrochloric acid.

7. Pharmaceutical composition according to one of claims 1 to 6, additionally containing one or more "absorption enhancer" in a concentration of 0.1% to 5% w/v.

8. Pharmaceutical composition according to one of claims 1 to 6, additionally containing a gel-forming agent in a concentration of 0.05% to 1% w/v to increase the viscosity.

9. Pharmaceutical composition according to one of claims 1 to 6, additionally containing a liposome-forming phospholipid in a concentration of 2% to 10% w/v and optionally additionally a hydrolysis product of a liposome-forming phospholipid in a concentration of 0.5% to 1% w/v.

10. Pharmaceutical composition according to one of the preceding claims, transferred under protective gas as individual doses into primary packaging means, the primary packaging means being placed in a secondary package in the form of a bag or tubular bag package made of aluminium, metallised film or transparent film, under a protective gas atmosphere, optionally together with an oxygen absorber.

11. Pharmaceutical composition according to one of the preceding claims, characterised in that the active substance is

1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine or

1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine.

12. Process for preparing a pharmaceutical composition according to one of the preceding claims, comprising the steps of

(a) dissolving 2 to 25% w/v, based on the pharmaceutical composition, of an active substance selected from the group (A) to (CJ) according to claim 1 in an aqueous solution, comprising

at least one equivalent of a physiologically acceptable solubilising acid or

(b) dissolving a salt of an active substance selected from the group (A) to (CJ) according to claim 1, formed with a physiologically acceptable solubilising acid, in water in an amount such that the active substance content of the composition based on the active substance is 2% to 25% w/v, and optionally

(c) adding excess physiologically acceptable solubilising acid and

(d) optionally adding one or more excipients, selected from absorption enhancers, gel-forming agents and liposome-forming phospholipids as well as

(e) optionally packaging the resulting solution under protective gas as single doses in primary packaging means, the primary packaging means being placed in a secondary package in the form of a bag or tubular bag packaging made of aluminium, metallised film or transparent film, under a protective gas atmosphere, optionally together with an oxygen absorber.

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